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Topical Administration of Antimicrobial Agents to Prevent Irradiation Mucositis of the Oral Cavity and Oropharynx: *A Pilot Study*

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SUMMARY The value of topical administration of antimicrobial agents to prevent irradiation mucositis of the oral cavity and oropharynx was investigated in this pilot study. Thirty-six patients receiving radiotherapy for head and neck cancer were included. Lozenges containing polymyxin E, tobramycin, and amphotericin B (PTA-lozenges) were administered during and after the course of irradiation to eradicate gram-negative bacilli and yeasts. Mucosal reactions and dysphagia were assessed and oropharyngeal cultures were obtained. Thirty-six patients treated in a previous period served as controls. Sixteen of the 36 patients in each group received irradiation predominantly to the oral mucosa. Confluent mucositis was observed in only 1 of 16 patients receiving PTA-lozenges but in 10 of the 16 patients of the control group ($P = 0.001$). Average duration of mucositis was also less with PTA-lozenges as well as dysphagia. Mucosal reactions and dysphagia in the patients who had mainly oropharyngeal mucosa in the treatment volume were not reduced. Persistent colonization by gram-negative bacilli occurred in only three patients. It is concluded that topical administration of polymyxin E, tobramycin, and amphotericin B may reduce irradiation mucositis of the oral cavity. The underlying mechanism must be further elucidated. *Radiat Oncol Invest* 1995;2:283-290. © 1995 Wiley-Liss, Inc.

Key words: radiotherapy, mucositis, prevention, gram-negative bacilli, head and neck cancer

INTRODUCTION

Irradiation mucositis is the most worrisome acute side effect of radiotherapy (RT) in the head and neck area and limits the rate at which fractionated irradiation can be delivered. It can cause severe discomfort to the patient with consequential weight loss, risk of dehydration, and loss of general physical and psychological well-being. In addition, severe mucositis may impose unplanned and undesired treatment interruption. Accelerated and

hyperfractionated radiation schedules result in increased acute mucosal reactions which often become dose limiting. Therefore, strategies to prevent or ameliorate radiation mucositis must be developed to allow further intensification of RT for head and neck carcinomas and to reduce discomfort to the patient.

Irradiation mucositis is basically the result of cell depletion caused by mitotic-linked cell death in the proliferating compartments of the epithelium.

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Consequent shortage of functional cells results in impaired tissue function accompanied by inflammatory changes. This inflammatory response to radiation damage may well be aggravated by secondary factors such as infectious processes.

Oral and oropharyngeal carriage of gram-negative bacilli is low in healthy individuals, varying from 3% to 18% in different studies [1–4]. Increased carriage has been reported in several groups of compromised patients, including patients with malignant disease [1,3,5]. During and after radiation for head and neck cancer gram-negative bacilli were more frequently isolated from the oral cavity and oropharynx than prior to treatment [6–8]. Eight of 14 patients who had undergone surgery for a tumor in the head and neck area were found to be persistently colonized with Enterobacteriaceae, Pseudomonadaceae or Acinetobacter species [4]. Spijkervet et al. [9] proposed that these gram-negative bacilli may enhance the mucosal radiation reaction, possibly through the production of endotoxins which are mediators of inflammation. They reported promising results in the prevention of irradiation mucositis through selective elimination of oral flora [9]. In patients who used lozenges containing 2 mg polymyxin E, 1.8 mg tobramycin, and 10 mg amphotericin B (PTA-lozenges) 4 times daily from the onset of a conventional irradiation course, eradication of the gram-negative bacilli was achieved after 3 weeks. Mucositis was significantly reduced in these patients when compared with patients who received chlorhexidine rinsing or placebo rinsing in an earlier study.

In a prospective, non-randomized pilot study, we administered these PTA-lozenges to patients receiving RT to the oral cavity and oropharynx. The aim was to expand the experience with selective elimination of oral flora to prevent irradiation mucositis and to determine whether it deserves testing on a larger scale. The results of this pilot study are presented here.

MATERIALS AND METHODS

Patients

From July 1991 till August 1992 36 consecutive patients were entered in the study after they had given informed consent (experimental group). All patients received external beam RT for head and neck cancer either as primary or as postoperative treatment. Only patients who received a total dose of 64 Gy or more to at least 50% of the mucosal surface of the oral cavity or oropharynx were included. Thirty-six patients treated between January 1989 and July 1991 served as historical controls

(control group). The institute's patient registration system was used to retrieve a control patient matching each individual patient of the experimental group with regard to tumor site, intention of treatment (primary or postoperative RT), and total dose delivered. The simulation film of this patient was then reviewed to ascertain whether, as in the patients of the experimental group, at least 50% of the mucosal surface of the oral cavity or oropharynx was irradiated to the full dose. The patient data of the registration system were searched starting at date July 1991 and went back in time until matching controls were found for all patients of the experimental group. Obviously, once a patient was selected as a control he or she could not be selected a second time. The age of the patients ranged from 40 to 85 years (median 61 years, mean 61 years) in the experimental group and from 36 to 78 years (median 61 years, mean 59 years) in the control group. Tumor sites, histology, TNM stage, radiation dose, and dental status are shown in Table 1.

Radiotherapy

Patients with oral cavity tumors were mostly operated and received postoperative RT, whereas patients with oropharyngeal tumors were generally treated by primary radiation. Almost all patients were treated with opposed lateral photon beams (4 and 6 MV) to the primary tumor site and upper neck nodes. The boost dose was delivered through reduced lateral and sometimes oblique opposed portals. The mid and lower neck nodes were treated through an anterior appositional photon field. In some cases a posterior field was added to supplement the dose in the posterior midcervical chain. Appositional electron beams of appropriate energy were used to boost nodal areas not included in the boost fields for the primary. Two patients with nasal cavity tumors were treated with three-field arrangements. The two patients with tumors of the cheek received treatment to the ipsilateral side only by appositional lateral fields using a combination of electrons and photons. Treatment was given once-a-day, 5 times/week, and in fractions of 2 Gy. Overall treatment time was 6.5–7 weeks and none of the patients had interruption of the treatment of more than 1 day. When RT was given as primary treatment, uninvolved nodal areas were treated to a dose of 44 Gy after which the primary tumor and neck metastases were boosted to a total dose of 68–70 Gy. In the postoperative situation the entire surgical bed was treated to 50 Gy followed by a boost of 14–20 Gy to areas at high risk for recurrence. Dose specification was according to Report

Table 1. Characteristics of Patients, Tumors, and Treatment for Control Group and Experimental Group, Separated by Mucosal Area Being Irradiated

| | No. of patients | | | |
|---|--|--------------------|--|--------------------|
| | $\geq 50\%$ of oral cavity mucosa irradiated | | $\geq 50\%$ of oropharyngeal mucosa irradiated | |
| | Control group | Experimental group | Control group | Experimental group |
| Total | 16 | 16 | 20 | 20 |
| Site of tumor | | | | |
| Oral cavity | 15 | 15 | — | — |
| Nasal cavity | 1 | 1 | — | — |
| Oropharynx | — | — | 15 | 15 |
| Nasopharynx | — | — | 5 | 5 |
| TNM stage (squamous cell carcinomas, UICC 1992) | | | | |
| Stage I | — | 2 | — | — |
| Stage II | 5 | 1 | — | 3 |
| Stage III | 4 | 3 | 8 | 7 |
| Stage IV | 5 | 8 | 11 | 8 |
| Other histologies | 2 | 2 | 1 | 2 |
| Histology | | | | |
| Squamous cell carcinoma | 14 | 14 | 18 | 18 |
| Lymphoepithelioma | — | — | 1 | — |
| Adenoid cystic carcinoma | — | — | 1 | — |
| Mucoepidermoid carcinoma | 1 | — | — | 1 |
| Carcinoma, undifferentiated | — | — | — | 1 |
| Rhabdomyosarcoma | — | 1 | — | — |
| Anaplastic small cell carcinoma | — | 1 | — | — |
| Melanoma | 1 | — | — | — |
| RT | | | | |
| Definitive | | | | |
| 68 Gy | — | — | 1 | 1 |
| 70 Gy | 2 | 2 | 17 | 17 |
| Postoperative | | | | |
| 64 Gy | 12 | 12 | 1 | 1 |
| 68 Gy | — | — | 1 | 1 |
| 70 Gy | 2 | 2 | — | — |
| Dental status | | | | |
| Dentulous | 9 | 6 | 8 | 8 |
| Edentulous | 7 | 10 | 12 | 12 |

29 of the International Commission on Radiation Units and Measurements (ICRU) [10].

Mucositis and Dysphagia Scoring

Weekly assessment of acute reactions started in the first week of treatment and continued until they had completely subsided, but at least until 2 weeks after completion of the course of radiation. Mucosal reactions and dysphagia were scored by two radiotherapists on a five-point scale (Table 2). In case of disagreement between the two observers, the highest score was used in the analysis. Acute mucositis was graded according to the system that was introduced by Fletcher et al. [11]: two grades of redness, studded fibrinous exudate, and confluent exudate. Since 1987 this scoring system has been applied routinely to all patients receiving RT to the head and neck area in our institute.

Table 2. Scores for Mucosal Reactions and Dysphagia

| Acute reactions | | Score |
|-----------------|---------------------------|-------|
| Mucosa | Normal | 0 |
| | Slight redness | 1 |
| | Severe redness | 2 |
| | Spotted mucositis | 3 |
| | Confluent mucositis | 4 |
| Dysphagia | No complaints | 0 |
| | Complaints, no medication | 1 |
| | Medication needed | 2 |
| | Liquid feeding | 3 |
| | Tube feeding | 4 |

Microbiological Techniques

Assessment of oral and oropharyngeal flora was done once before the start of RT and before admin-

istration of PTA-lozenges. This was repeated weekly during the course of radiation and until 2 weeks thereafter. Oral and oropharyngeal cultures were obtained by oral washing with isotonic saline. Each rinse was centrifuged, the supernatant discarded, and the pellet resuspended, which was then inoculated semiquantitatively on non-selective sheep blood agar (Mast Diagnostics Ltd., Morsey-side, UK), Sabouraud agar (BBL: Becton Dickinson Microbiology Systems, Cockeysville, MD) for yeasts, mannitol-salt agar (Oxoid, Basingstroke, Hampshire, UK) for staphylococci, and eosin methylene blue agar (BBL) for aerobic and facultative anaerobic gram-negative bacilli. The Sabouraud agar plates were incubated for 96 hr at 29°C aerobically. The other plates were incubated for 48 hr at 37°C in 10% carbon dioxide. Enterobacteriaceae were identified by the Analytical Profile Index (API 20E system, bioMérieux S.A., Marcy l'etoile, France). The detection level for gram-negative bacilli was 10^2 colony forming units/ml. Patients were considered to be carriers of a particular microorganism when a minimum of two consecutive rinses were positive for that microorganism. No cultures were obtained from patients in the historical control group.

Oral Hygiene

All patients received the same treatment and instruction on oral hygiene including:

- Oral and dental examination by the oral surgeon, dentist, and oral hygienist. Dental treatment to eliminate foci of infection or mechanical irritation was performed.
- Weekly cleansing of the oral cavity, instruction to maintain oral hygiene, and brush training by the oral hygienist.
- Rinsing of the oral cavity and oropharynx with salt-soda solution 6–8 times daily.
- Daily application of neutral 1% sodium fluoride gel with custom-made carriers in dentate patients.
- Edentulous patients were not allowed to wear their prostheses during the course of irradiation.

PTA-Lozenges

Lozenges containing 2 mg polymyxin E, 1.8 mg tobramycin, and 10 mg amphotericin B were taken 4 times daily by patients of the experimental group. Administration started 2 days before initiation of RT and was continued until 2 weeks after completion of RT.

Statistics

Fisher's exact probability test was used to test the significance of differences in mucosa and dyspha-

gia scores as well as numbers of positive cultures between treatment groups. Average durations of mucosal reactions and dysphagia were compared by the t-test.

RESULTS

Mucositis

Sixteen of the 36 patients of both the experimental group and the control group received irradiation predominantly to the oral mucosa. The remaining 20 patients of both groups had mainly oropharyngeal mucosa in the treatment volume. Irradiation of the oral mucosa produced confluent mucositis in only 1 of the 16 patients receiving PTA-lozenges but in 10 of 16 patients of the control group ($P = 0.001$, Fisher's exact test). Seven of 16 patients of the experimental group vs. all patients of the control group developed spotted mucositis ($P < 0.001$, Fisher's exact test). If spotted or confluent mucositis occurred, the average duration was 21 days (standard deviation 16 days) in the experimental group and 36 days (standard deviation 16 days) in the control group ($P = 0.04$, t-test). On average, the first signs of fibrinous exudate were observed 8 days later in the experimental group compared to the control group. Figure 1 shows the scores for mucosal reactions of the oral cavity in the control group (Fig. 1A) and the experimental group (Fig. 1B). Seventy-eight percent (31/40) of patients irradiated predominantly to the oropharyngeal mucosa developed confluent mucositis with no significant difference between the experimental and control groups. Severity of mucositis was comparable in dentulous and edentulous patients.

Dysphagia

Dysphagia scores show a similar pattern for the various groups and subgroups although differences are not as evident as for mucosal reactions (Fig. 2). Although not statistically significant, PTA-lozenges did seem to reduce the severity of dysphagia produced by irradiation of the oral mucosa. Only half (8/16) of the patients of the experimental group vs. 13 of 16 patients of the control group needed analgetics ($P = 0.14$, Fisher's exact test). Eighty-five percent (34/40) of patients irradiated predominantly to the oropharynx required analgetics with no significant difference between the experimental and control groups.

Oral and Oropharyngeal Flora

Before the start of RT gram-negative bacilli were isolated from rinses of 6 patients (17%). Eleven patients in whom initial rinses showed no growth

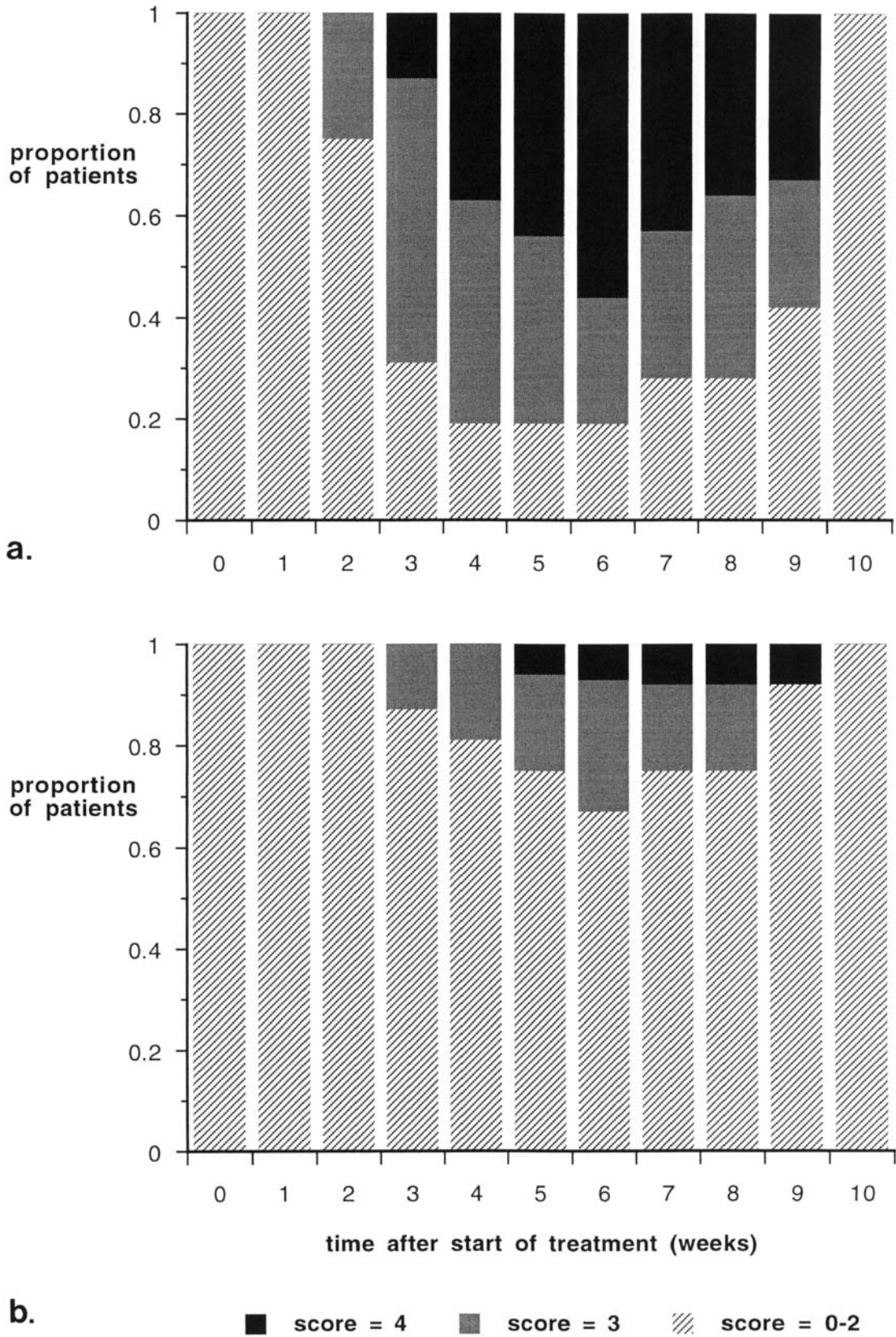


Fig. 1. Scores for mucosal reactions during and after RT of patients irradiated predominantly to the oral cavity. **a:** Control group. **b:** Experimental group.

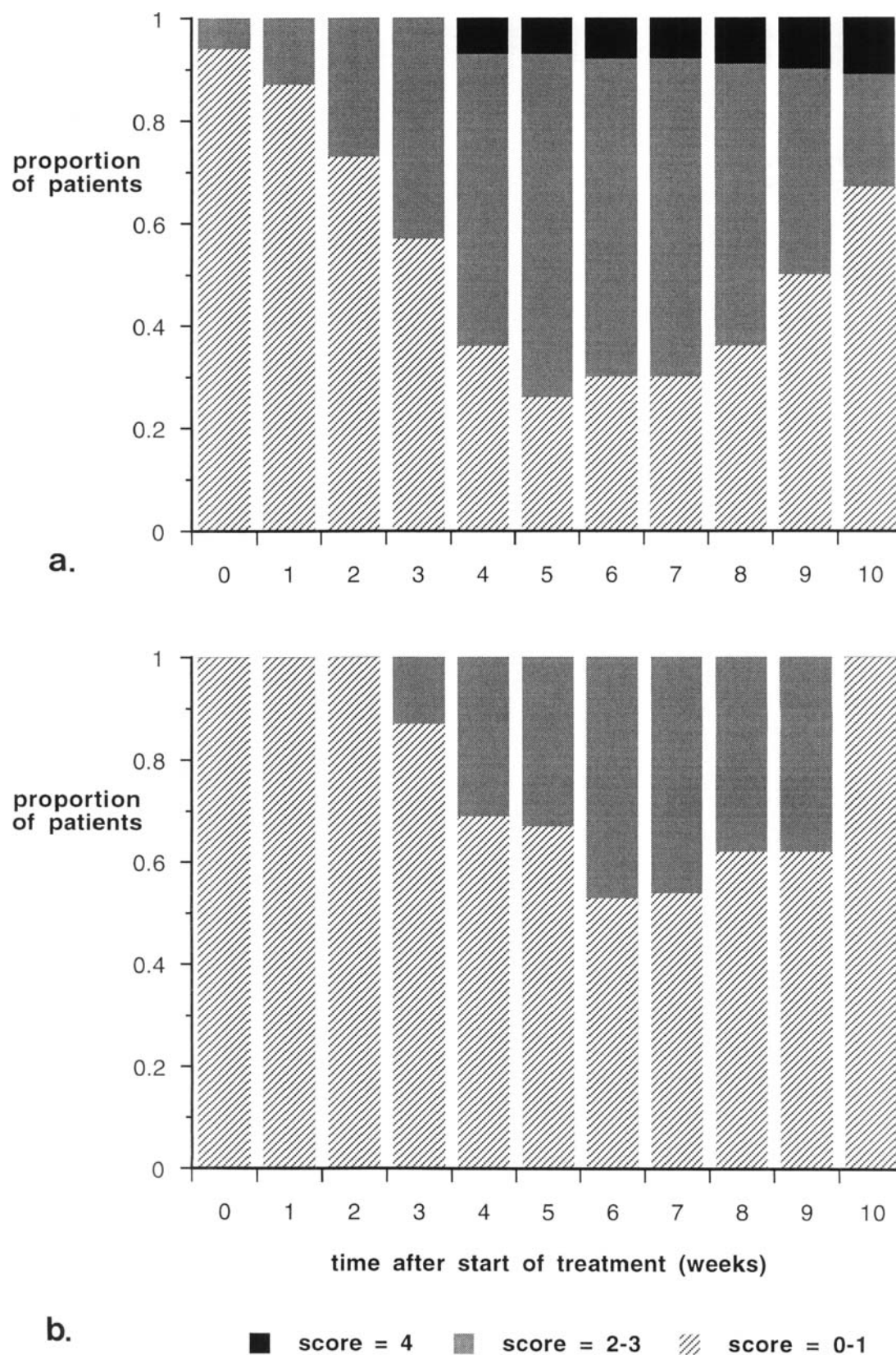


Fig. 2. Scores for dysphagia during and after RT of patients irradiated predominantly to the oral cavity. **a:** Control group. **b:** Experimental group.

had one or more positive rinses after the start of RT. In total, gram-negative bacilli could be isolated from 17 of the 36 patients at one or more occasions, from 9 of 16 patients who were irradiated mainly to the oral cavity, and from 8 of 20 who received treatment predominantly to the oropharynx. The frequency of isolation of gram-negative bacilli did not decrease until after the completion of RT. However, of all patients only three had two or more consecutive rinses showing growth of the same species and could be considered carriers. Yeasts, mostly candida, were found in the rinses of 14 of the 36 patients (39%) at the onset of treatment. Eight of them also had subsequent positive rinses. Ten patients who were initially negative became positive during or after the course of radiation. Thus, a total of 24 patients had yeasts isolated from their mouth or throat: 13 of the 16 irradiated to the oral cavity and 11 of 20 irradiated to the oropharynx. There was a gradual decrease of the number of positive rinses during the treatment to 3/36 (8%) after completion of treatment.

DISCUSSION

Selective modulation of oral and oropharyngeal flora was attempted through topical application of polymyxin E, tobramycin, and amphotericin B. The combination of the two antibiotics has bactericidal activity against most gram-negative species. They are non-absorbable and the mode of administration, i.e., lozenges, ensures sufficiently long contact time [9]. Amphotericin B is active against yeasts.

The prevalence of gram-negative bacilli in oral and pharyngeal cultures from patients with advanced cancer has been reported by Jobbins et al. [5] to be as high as 49%. Spijkervet [4] observed colonization in 57% of patients who had undergone surgery for a tumor in the head and neck area. In our study the prevalence of gram-negative bacilli prior to RT was 17%, which is low compared to what is reported by the other investigators. However, our patients were not hospitalized and probably had less advanced disease than those studied by Jobbins et al. [5]. Another potential factor contributing to this difference may be the technique of culturing. Preincubation of samples in a selective broth gives a higher yield of gram-negative bacilli than direct plating as was done in our study [3,4]. This increase can be up to a factor of three [3]. At the onset of treatment yeasts, mostly candida, were isolated from 39% of our patients. This is in good agreement with observations by others [12–14]. With use of PTA-lozenges there was a gradual decrease of positive patients to 8% after completion of RT.

Seventy-eight percent of patients irradiated predominantly to the oropharyngeal mucosa developed confluent mucositis. This corresponds to what generally can be expected when this region is irradiated with a conventional fractionation schedule to a total dose of 68–70 Gy [15]. There was no difference between the experimental group and the control group. When radiation was directed mainly to the oral cavity severity of mucositis was significantly less in patients receiving PTA-lozenges when compared to the control group. Also dysphagia was less although this difference was not statistically significant. These patients differed in two major aspects from those who received irradiation predominantly to the oropharynx. First, obviously the sites of tumor location and thus the regions that were treated differed. Second, 14 of the 16 patients irradiated to the oral cavity previously had surgery, whereas RT was the primary treatment for 18 of the 20 patients who had the tumor located in or near the oropharynx.

The remarkable mildness of mucosal reactions when PTA-lozenges were prophylactically administered suggests that microorganisms and specifically gram-negative bacilli can aggravate radiation mucositis in the oral cavity. This was postulated by Spijkervet et al. [9], who observed merely redness as the most severe sign of irradiation mucositis in 15 head and neck cancer patients using PTA-lozenges. In their study this was associated with successful elimination of oral gram-negative bacilli, i.e., significant reduction of carriage after 3 weeks of treatment. Twelve of the 15 patients received postoperative RT using a conventional schedule to total doses of 66–70 Gy. These patients are thus comparable to the subgroup from our study that seems to benefit from PTA-lozenges. Complete eradication of gram-negative bacilli was not achieved in our study but carriage occurred in only three patients. From the other patients gram-negative bacilli were isolated incidentally. This may reflect temporary presence of these bacilli which can have been acquired from food or beverage [16,17] and which may be subsequently eliminated by the antibiotic treatment. Due to the technique of culturing, patients carrying low quantities of gram-negative bacilli may have been falsely identified as negative. Assuming that these low quantities are easier to eliminate, the effectiveness of the antibiotics with regard to prevention of carriage of these particular microorganisms may thus have been underestimated. The analysis is complicated by the fact that no cultures from the historical controls were available.

Interestingly, the antimicrobial prophylaxis seemed effective only in the oral cavity. Whether

this truly reflects a difference between anatomic sites is not clear. Other strains than the gram-negatives may have a role in the oropharynx or microorganisms in general may only minimally affect the radiation response of the oropharyngeal mucosa. Most of the patients who showed benefit from the antimicrobial prophylaxis, both in the study by Spijkervet et al. [9] and in our study, underwent surgery prior to radiation. This may have altered the colonization defense mechanisms through manipulations in the oral cavity or through less specific mechanisms. The latter is supported by the observation that gram-negative carriage was enhanced in relatively young patients who had undergone orthopedic operations [1].

It is concluded that this pilot study confirms the results of Spijkervet et al. [9]. Topical administration of polymyxin E, tobramycin, and amphotericin B may prevent severe irradiation mucositis of the oral cavity. Further testing in a randomized, placebo-controlled study is warranted. The role of microorganisms in the pathogenesis of irradiation mucositis must be further elucidated.

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